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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
22393 WO-WJ		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP2005/003348	31/03/2005	01/04/2004
Applicant		
F.HOFFMANN-LA ROCHE AG		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 8 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
      [ ] The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
   b. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box II).

3. [ ] **Unity of invention is lacking** (see Box III).

4. With regard to the **title,**
   [ ] the text is approved as submitted by the applicant.
   [X] the text has been established by this Authority to read as follows:

   CYCLODEXTRIN INCLUSIONS COMPLEXES OF PYRIMIDINE-2,4,6-TRIONES

5. With regard to the **abstract,**
   [ ] the text is approved as submitted by the applicant.
   [X] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. 1
      [X] as suggested by the applicant.
      [ ] as selected by this Authority, because the applicant failed to suggest a figure.
      [ ] as selected by this Authority, because this figure better characterizes the invention.
   b. [ ] none of the figures is to be published with the abstract.

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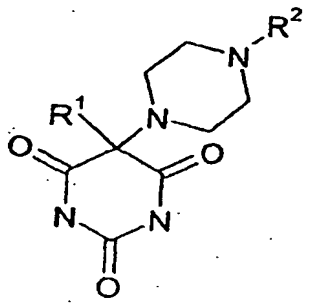
Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

It was surprisingly found that a trioxopyrimidine-cyclodextrin complex formed of a trioxopyrimidine derivative represented by the below-described formula (I) and a water-soluble cyclodextrin (further abbreviated as CD) exhibits enhanced water solubility, excellent stability, and low topical stimulation and is useful as a therapeutic agent.

Accordingly, the present invention provides a trioxopyrimidine-cyclodextrin complex formed of a trioxopyrimidine derivative or a salt thereof and a cyclodextrin, preferably α-, β- or γ-cyclodextrin or a water-soluble cyclodextrin derivative (water-soluble being defined as a solubility of at least 0.5 gr/100ml water at 25°C), wherein the trioxopyrimidine derivative is represented by formula (I).



(I)

It was furthermore found that such a trioxopyrimidine complex with cyclodextrin and an adjuvant such as L-lysine or L-arginine show improved water solubility and bioavailability, excellent stability, and low topical stimulation and is useful as a therapeutic agent.

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A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K47/48 A61K31/515 A61P11/06 A61K31/198 A61K47/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, EMBASE, CHEM ABS Data, DISSERTATION ABS, CANCERLIT

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 01/25217 A (HOFFMANN LA ROCHE) 12 April 2001 (2001-04-12) cited in the application examples 1,3.1,3.7,3.15 -----	1-10
Y	WO 97/23465 A (BOEHRINGER MANNHEIM GMBH ; BOSIES ELMAR (DE); ESSWEIN ANGELIKA (DE); G) 3 July 1997 (1997-07-03) cited in the application example 26 ----- -/--	1-10

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 June 2006	26. 06. 2006

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Dullaart, A

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Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GRAMS F ET AL: "PYRIMIDINE-2,4,6-TRIONES: A NEW EFFECTIVE AND SELECTIVE CLASS OF MATRIX METALLOPROTEINASE INHIBITORS" BIOLOGICAL CHEMISTRY, vol. 382, no. 8, August 2001 (2001-08), pages 1277-1285, XP008009641 ISSN: 1431-6730 cited in the application the whole document	1-10
Y	WO 02/089824 A (HOFFMANN LA ROCHE ; FRIESS THOMAS (DE); SCHEUER WERNER (DE); KRELL HAN) 14 November 2002 (2002-11-14) figures tables claims	1-10
Y	FOLEY L H ET AL: "Novel 5,5-disubstitutedpyrimidine-2,4,6-triones as selective MMP inhibitors" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 11, no. 8, 23 April 2001 (2001-04-23), pages 969-972, XP002271775 ISSN: 0960-894X the whole document	1-10
Y	MASAHIKO SUZUKI ET AL: "A STUDY OF 1:1 PLUS 1:2 COMPLEXES BETWEEN BARBITURATE AND CYCLODEXTRIN USING THE FREEZING POINT DEPRESSION METHOD" CHEMICAL AND PHARMACEUTICAL BULLETIN, TOKYO, JP, vol. 41, no. 8, 1 August 1993 (1993-08-01), pages 1444-1447, XP000395593 ISSN: 0009-2363 abstract tables 1,2 page 1447	1-10
Y	WO 00/40962 A (KOSAK KEN M) 13 July 2000 (2000-07-13) claim 1	1-10
Y	JOZSEF SZEJTLI: "CYCLODEXTRIN TECHNOLOGY" 1988, KLUWER ACADEMIC PUBLISHERS , DORDRECHT, NL , XP001194813 page 186 - page 306	1-10

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Y	AKI HATSUMI ET AL: "Multimodal inclusion complexes between barbiturates and 2-hydroxypropyl-beta-cyclodextrin in aqueous solution: Isothermal titration microcalorimetry, 13C NMR spectrometry, and molecular dynamics simulation" JOURNAL OF PHARMACEUTICAL SCIENCES, vol. 90, no. 8, August 2001 (2001-08), pages 1186-1197, XP002297398 ISSN: 0022-3549 abstract figures tables	1-10
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Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	CSABAI KATALIN ET AL: "Interaction of some barbituric acid derivatives with hydroxypropyl-beta-cyclodextrin" INTERNATIONAL JOURNAL OF PHARMACEUTICS, vol. 91, no. 1, 1993, pages 15-22, XP001202117 AMSTERDAM, NL ISSN: 0378-5173 abstract tables figures page 20, right-hand column - page 21, right-hand column, last line	1-10
Y	LEIN, MICHAEL ET AL: "The new synthetic matrix metalloproteinase inhibitor (roche 28-2653) reduces tumor growth and prolongs survival in a prostate cancer standard rat model" ONCOGENE, vol. 21, no. 3, 2002, pages 2089-2096, XP002297399 ISSN: 0950-9232 the whole document	1-10
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Y	MURA P ET AL: "Ternary systems of naproxen with hydroxypropyl-[beta]-cyclodextrin and aminoacids" INTERNATIONAL JOURNAL OF PHARMACEUTICS 24 JUL 2003 NETHERLANDS, vol. 260, no. 2, 24 July 2003 (2003-07-24), pages 293-302, XP002383360 ISSN: 0378-5173 abstract page 295; table 1 page 300, right-hand column, paragraph CONCLUSION - page 301, right-hand column -----	1-10
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